part of this substance was recrystallized from EtOAc; the pure orange crystals melted at 166° dec. *Anal.* ($C_6H_4Br_2N_2S$) C, H, N.

trans-**2-Bromo(4-nitrobenzenesulfonamido)cyclohexane (I).**—N,N-Dibromo-4-nitrobenzenesulfonamide (10 g) was added to a mixture of cyclohexene (30 ml) and CCl_4 (15 ml). A white precipitate appeared with slight evolution of heat. After the exothermic reaction subsided, the mixture was refluxed for 2.5 hr, and the precipitate was filtered with suction. Recrystallization (EtOH) gave colorless needles, mp 170–171°, yield 8.8 g (87.3%). *Anal.* ($C_{12}H_{15}BrN_2O_4S$) C, H, N.

trans-**2-Ethoxy-1-(4-nitrobenzenesulfonamido)cyclohexane (III).**—2-Bromo-1-(4-nitrobenzenesulfonamido)cyclohexane (I) (3 g) was added to a solution of Na (0.2 g) in absolute EtOH (30 ml). The mixture was refluxed on a steam bath for 2 hr. After the solution was cooled, 3.5% HCl (9.1 ml) was added and allowed to stand to yield 2.1 g (75%) of pale yellow needles, mp 140–141° (from MeOH). *Anal.* ($C_{14}H_{20}N_2O_5S$) C, H, N.

N-(4-Nitrobenzenesulfonyl)cyclohexenimine (II).—Dried Ag_2O (prepared from 3 g of $AgNO_3$), I (2 g), and Me_2CO (25 ml) were mixed and refluxed for 6 hr. The precipitate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized (C_6H_6) giving pale yellow needles, mp 133–136°, yield 1.25 g (80.7%). This compound was also obtained by the treatment of I with AgOAc in C_6H_6. *Anal.* ($C_{12}H_{14}N_2O_4S$) C, H, N.

trans-**2-Acetoxy-1-(4-nitrobenzenesulfonamido)cyclohexane (IV).**—A mixture of II (0.5 g) and AcOH (3 ml) was refluxed for 3 hr. After cooling, H_2O (2 ml) was added; the white precipitate was recrystallized (EtOH) yielding yellow granules, 0.55 g (90%), mp 157–158°. *Anal.* ($C_{14}H_{18}N_2O_6S$) C, H, N.

trans-**2-Chloro-1-(4-nitrobenzenesulfonamido)cyclohexane (V).**—A mixture of II (0.564 g) and 13% HCl (4.2 ml) was refluxed for 3 hr. After cooling, the precipitate was collected and recrystallized (EtOH), mp 150–151°, yield 0.574 g (89%). *Anal.* ($C_{12}H_{15}ClN_2O_4S$) C, H, N.

Catalytic Reduction of Nitro Compounds I, III-V.—These compounds were reduced catalytically in EtOH (PtO_2) to the corresponding amino compounds (VI–IX, respectively) in good yields as follows: VI, mp 174–175° [*Anal.* ($C_{12}H_{17}BrN_2O_2S$) C, H, N]; VII, mp 105–106° [*Anal.* ($C_{14}H_{22}N_2O_3S$) C, H, N]; VIII, mp 157–158° [*Anal.* ($C_{14}H_{20}N_2O_4S$) C, H, N]; IX, mp 159–160° [*Anal.* ($C_{12}H_{17}ClN_2O_2S$) C, H, N]. VI was treated with Ac_2O to give *trans*-2-bromo-1-(4-acetamidobenzenesulfonamido)cyclohexane (X), mp 179–180° [*Anal.* ($C_{14}H_{19}BrN_2O_3S$) C, H, N].

Studies in Cinnoline Chemistry. I. The Synthesis of Substituted Phenyl Cinnolyl Sulfides

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Cinnoline compounds have been recommended as drugs in the chemotherapy of trypanosomiasis,[1] as bactericides and antiparasites,[2] and in antitumor screening.[3] The antileukemic activity of various 4-substituted benzylthiocinnolines reported by Castle and his coworkers[4] aroused our interest in preparing a series of substituted phenyl cinnolyl sulfides and subjecting them for pharmacological screening. This paper describes the preparation of some new substituted-phenyl cinnolyl sulfides.

(1) J. R. Keneford, E. M. Lonrie, J. S. Morley, J. C. E. Simpson, J. Williamson, and P. H. Wright, *J. Chem. Soc.*, 2595 (1952).

(2) E. P. Taylor, M. D. Potter, H. O. J. Collier, and W. C. Austin, British Patent 812,994 (May 6, 1959); *Chem. Abstr.*, **53**, 18971 (1959).

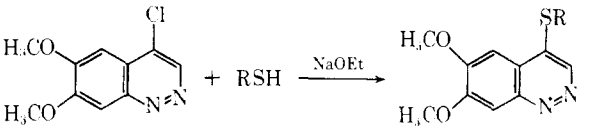
(3) R. N. Castle, H. Ward, N. White, and K. Adachi, *J. Org. Chem.*, **25**, 570 (1960).

(4) R. N. Castle, K. Adachi, and W. D. Guither, *J. Heterocyclic Chem.*, **2**, 459 (1965).

Experimental Section[5]

General Procedure.—The method is illustrated with the preparation of 2-chlorophenyl 4-(6,7-dimethoxycinnolyl) sulfide. To a dry solution of NaOEt from Na (0.02 g-atom) in absolute EtOH (20 ml) under N_2 was added with shaking *o*-chlorothiophenol (0.02 mole) followed by addition of 0.02 mole of 4-chloro-6,7-dimethoxycinnoline.[6] The reaction mixture was refluxed for 2 hr under N_2, diluted with sufficient H_2O, and made alkaline to dissolve the unreacted thiophenol. The solid material was filtered and recrystallized from dilute EtOH: mp 164–165°, yield 1.5 g. Compounds prepared in this way are listed in Table I.

TABLE I



No.	R	Yield,[a] %	Mp, °C	Formula[b]
1	C_6H_5	72	165	$C_{16}H_{14}N_2O_2S$
2	*p*-$CH_3C_6H_4$	94	181–182	$C_{17}H_{16}N_2O_2S$
3	*o*-ClC_6H_4	75	152	$C_{16}H_{13}ClN_2O_2S$
4	*m*-ClC_6H_4	34	176–177	$C_{16}H_{13}ClN_2O_2S$
5	*p*-ClC_6H_4	47	199	$C_{16}H_{13}ClN_2O_2S$
6	2,5-$Cl_2C_6H_3$	67	200–201	$C_{16}H_{12}Cl_2N_2O_2S$
7	3,5-$Cl_2C_6H_3$	58	177–178	$C_{16}H_{12}Cl_2N_2O_2S$
8	3,4-$Cl_2C_6H_3$	68	192	$C_{16}H_{12}Cl_2N_2O_2S$[c]

[a] All compounds were recrystallized from EtOH–H_2O. [b] All compounds were analyzed satisfactorily for C, H, N. [c] This compound was analyzed satisfactorily for C, H.

Acknowledgment.—Thanks are due to Professor S. Siddappa for his interest in the work. One of us (S. M. Y.) is grateful to the University Grants Commission, New Delhi, India, for a Research Training Scholarship. We thank Mr. V. A. Desai and Mr. R. S. Inamdar for the analytical data recorded.

(5) Melting points were taken in capillary tubes and are uncorrected.

(6) R. N. Castle and F. H. Kruse, *J. Org. Chem.*, **17**, 1571 (1952).

N,N,N′,N′-Tetraalkylhomopiperazinium Salts[1]

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The availability of homopiperazine (1,4-diazacycloheptane) by a novel and simple synthesis[2] has made it possible to prepare a series of symmetrical N,N′-dialkylhomopiperazines and their quaternary ammonium salts. The bis-quaternary dimethosulfates were prepared for the purpose of determining their bactericidal properties in comparison with homologous compounds derived from N,N′-dialkylpiperazines and with N-alkyl-N-methylpyrrolidinium methosulfates and N-alkyl-N-methylmorpholinium and -thiamorpholinium methosulfates previously described.[3]

Experimental Section[4]

Symmetrical N,N′-dialkylhomopiperazines (Table I) were prepared by refluxing 5 g (0.05 mole) of homopiperazine with

(1) Abstracted in part from the thesis of K. E. Jones presented to Lafayette College in partial fulfillment of the requirements for the degree of B.S. in Chemistry, June 1964.

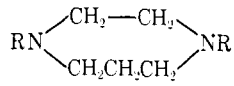
(2) F. Poppelsdorf and R. C. Myerly, *J. Org. Chem.*, **26**, 131 (1961).

(3) (a) D. R. Smith, J. W. Curry, and R. L. Eiffert, *J. Am. Chem. Soc.*, **72**, 2969 (1950); (b) W. F. Hart and M. E. McGreal, *J. Org. Chem.*, **22**, 84 (1957); (c) *ibid.*, **22**, 87 (1957), and references cited therein.

(4) Melting points were taken in capillary tubes and are corrected. Elemental analyses were determined by Drs. Weiler and Strauss, Oxford, England. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical value.

TABLE I

SYMMETRICAL N,N′-DIALKYLHOMOPIPERAZINES



R	Yield,[a] %	Bp (mm) or mp, °C	Formula	Analyses
n-$C_{10}H_{21}$		150–152 (3)	$C_{25}H_{52}N_2$	C, H, N
n-$C_{12}H_{25}$	34	10	$C_{29}H_{60}N_2$	H, N; C[b]
n-$C_{14}H_{29}$	45	32–33	$C_{33}H_{68}N_2$	C, H, N
n-$C_{16}H_{33}$	72	41–42	$C_{37}H_{76}N_2$	C, H, N
n-$C_{18}H_{37}$	74	47–48	$C_{41}H_{84}N_2$	C, H, N

[a] Yield calculated after one recrystallization. [b] C: calcd, 79.74; found, 79.04.

0.11 mole of the alkyl bromide in 50 ml of EtOH for 3 hr. After cooling, the resultant salt was filtered and washed (cold EtOH). The salt was suspended in 50% EtOH and a slight excess of 20% KOH solution was added. Upon warming, the free amine separated as a colorless oil, which was separated by extracting three times with C_6H_6. The C_6H_6 extracts were distilled *in vacuo* to remove EtOH and H_2O. The residue was taken up in warm C_6H_6 and filtered through hard paper and the solvent again was removed *in vacuo*. The residue was taken up in Me_2CO and recrystallized from this solvent. The dialkylhomopiperazines are white, waxy solids or colorless oils, insoluble in H_2O and only slightly soluble in EtOH and EtOAc. The yields obtained varied from 35 to 75%.

N,N′-Dialkyl-N,N′-dimethylhomopiperazinium dimethosulfates (Table II) were prepared by dissolving 0.0025 mole of the dialkylhomopiperazine in EtOH (10 ml), adding 0.006 mole of redistilled Me_2SO_4, and refluxing for 3 hr. The reaction mixture was chilled and filtered and the product was recrystallized from EtOH and dried *in vacuo*. The yields obtained varied from 55 to 88%. The dimethosulfates are white, waxy solids insoluble in Et_2O and only slightly soluble in cold EtOH and EtOAc.

TABLE II

SYMMETRICAL N,N′-DIALKYL-N,N′-DIMETHYLHOMOPIPERAZINIUM DIMETHOSULFATES AND DIMETHIODIDES

	Dimethosulfates			Dimethiodides	
R	Yield,[a] %	Mp, °C dec	Formula[b]	Mp, °C	Formula[b]
n-$C_{10}H_{21}$	55	260–262	$C_{29}H_{64}N_2O_8S_2$[c]	214–216	$C_{27}H_{58}I_2N_2$
n-$C_{12}H_{25}$	69	263	$C_{33}H_{72}N_2O_8S_2$	206–207	$C_{31}H_{66}I_2N_2$
n-$C_{14}H_{29}$	83	258–259	$C_{37}H_{80}N_2O_8S_2$	214	$C_{35}H_{74}I_2N_2$
n-$C_{16}H_{33}$	88	261–265	$C_{41}H_{88}N_2O_8S_2$	218–222	$C_{39}H_{82}I_2N_2$
n-$C_{18}H_{37}$	86	250–252	$C_{45}H_{96}N_2O_8S_2$	195–197	$C_{43}H_{90}I_2N_2$

[a] Yield calculated after one recrystallization. [b] All compounds were analyzed for C, H, N. [c] C: calcd, 54.68; found, 54.18.

N,N′-Dialkyl-N,N′-dimethylhomopiperazinium dimethiodides (Table II) were prepared by dissolving 0.0025 mole of the dialkylhomopiperazine in EtOH (10 ml), adding 0.0075 mole of MeI, and refluxing for 3 hr. The product was filtered from the chilled reaction mixture, recrystallized twice from EtOH, and dried *in vacuo*. These bis-quaternary salts are light yellow in color, insoluble in H_2O, and only slightly soluble in EtOH, Me_2CO, and EtOAc. The yields obtained were nearly quantitative.

Acknowledgment.—Thanks are due to Dr. R. C. Myerly of the Union Carbide Chemicals Company for the homopiperazine used in this work.

Book Reviews

Medical Research: A Series of Monographs. Volume 2. Drugs Affecting the Central Nervous System. Edited by ALFRED BURGER. Marcel Dekker, Inc., New York, N. Y. 1968. xv + 437 pp. 16 × 24 cm. $19.75.

This is the second volume of a series dealing with the subject of neuropharmacology. The first volume considered those families of drugs acting specifically upon the peripheral nervous system; this present volume surveys those drugs which act directly upon the central nervous system. In keeping with the style of the first volume, the reviews and monographs collected represent discussions of fundamental rather than of applied pharmacology. The eight chapters of this volume range from general and comprehensive reviews of classes of central nervous system drug effects, to the specific and detailed minutiae of narrow chemical systems having CNS action.

At the general review end of the spectrum, there is a compact and complete chapter on the subject of narcosis and anesthesia by Larsen, Van Dyke, and Chenoweth of The Dow Chemical Company, wherein the treatment of a diverse group of chemicals is unified through the consideration of common mechanisms. Domino, Hudson, and Zografi discuss the frequently reviewed field of phenothiazines from the point of view of biochemical and pharmacological modes of action. A compilation of the many chemical types that may be grouped under the title psychotomimetic agents has been made by Hofmann, and both their medical and their paramedical uses are discussed. A broad chemical review by Donahoe and Kimura compares the wide range of families of agents effecting skeletal muscle relaxation through central nervous system action. This chapter serves as a useful companion piece to the chapter in Volume 1 that discusses similar pharmacological consequences through action in the area of the myoneural junction. A general review of the diverse types of drugs effective in the treatment of mental depression has been assembled by Biel.

The remaining chapters deal with minor topics in fine detail. Sternbach, Randall, Banziger, and Lehr of Hoffmann-La Roche present a thorough structure–activity relationship study of the 1,4-benzodiazepine analogs of Librium and Valium; however, their conclusions derive from animal screening data, and there is no extrapolation to human effectiveness. Similarly, Janssen and Van der Eycken present an overwhelming amount of detail, with archival thoroughness, on a series of compounds chemically related to, and pharmacologically more potent than, morphine. Lastly, Abood reviews the family of atropine-like glycolate esters, with special emphasis on the interrelationship between their structures and their mechanism of action. Issue may be taken with the employment of the term "psychotomimetic" in his title of this review of highly active anticholinergic drugs, for this usage conflicts with the generally accepted definition given by Hofmann.

All in all, this volume is an excellent reference work and will be of value to all scientists in this field. The printing is clear, the chemical formulas are free from typographical error to an unprecedented degree, and the subject and author indexes are extensive and complete. The appearance of the next volume of this set, concerning pharmacological testing methods, should complete a trilogy indispensible to anyone active in this area of research.

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